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Mechanistic Studies on the N-Alkylation of Amines with Alcohols Catalysed by Iridium(I) Complexes with Functionalised N-Heterocyclic Carbene Ligands

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Iridium(I)-cyclooctadiene complexes featuring O- and N-donor functionalised NHC ligands efficiently catalyse the C–N coupling of amines with alcohols through a borrowing hydrogen mechanism. These catalysts have been applied for the N-alkylation of several aromatic and aliphatic primary amines with a range of alcohols including benzyl alcohol derivatives, straight chain primary alcohols and secondary alcohols. The cationic complex $[\text{Ir}(\text{NCCCH}_3)(\text{cod})\{\text{Melm}(2\text{-methoxybenzyl})\}]^+$ (cod = 1,5-cyclo-octadiene, Melm = 3-methylimidazol-2-ylidene) having a rigid O-donor wingtip exhibit the best catalyst performance for the N-alkylation of aniline with benzyl alcohol giving quantitative conversion to N-benzylaniline in 3 h. Experimental and theoretical studies at DFT level on the N-alkylation of aniline with benzyl alcohol catalysed by the model compound $[\text{IrCl}(\text{cod})(\text{IME})]$ (IME = 1,3-dimethyl-imidazol-2-ylidene) support the participation of the iridium catalyst not only in the alcohol dehydrogenation and imine hydrogenation steps but also in the key step leading to the formation of the new C–N bond. Nucleophilic attack of an iridium-amido species generated in basic medium on the electrophilic aldehyde results in a hemiaminal intermediate species from which the hemiaminal is released by alcoholysis. The free hemiaminal dehydrates to give the corresponding intermediate imine product that is hydrogenated by the iridium catalyst to the N-alkylated amine product. The iridium(I) complexes featuring functionalised NHC ligands are more active than $[\text{IrCl}(\text{cod})(\text{IME})]$ which highlights the positive influence of the functional group on the N-alkylation catalytic activity.

1. Introduction

The development of efficient and environmentally benign catalytic strategies for C–N bond formation is an important goal in organic chemistry. In particular, the synthesis of N-substituted amines from alcohols plays an important role in the production of bulk and fine chemicals such as pharmaceuticals, polymers, or agrochemicals.^[1] Transition metal-catalysed N-alkylation of amines by alcohols based on a so-called *hydrogen autotransfer* or *borrowing hydrogen*^[2] methodology has attracted much attention in recent years. Conventional non-catalytic transformations of alcohols into amines generally first require the introduction of a suitable

leaving group followed by nucleophilic substitution. These multistep pathways suffer from low atom economy, production of stoichiometric amounts of waste products and limited selectivity. On the contrary, the N-alkylation of amines with alcohols following the borrowing hydrogen approach has the advantage of using available, less toxic and inexpensive starting materials, producing water as the only by-product, and so this powerful catalysis strategy has significantly expanded during the last past decade.^[3]

Conversion of alcohols into amines by borrowing hydrogen catalysis is seen as an interesting tandem extension within the field of transfer hydrogenation as an intermediate carbonyl compound is formed by hydrogen-transfer dehydrogenation of the alcohol and the final amine product is obtained by hydrogenation of the in situ generated imine intermediate, both with the participation of metal hydride catalytic species (Chart 1). A wide range of homogeneous transition metal-based catalysts accomplishes this domino process and current research focuses on the development of more efficient catalysts for performing the reactions under mild conditions.^[4] Current advances in the

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field include the development of heterogeneous catalysts,^[5] earth abundant element-based catalysts^[6] or transition metal-free highly chemoselective catalytic systems^[7] but only a few systems are able to perform asymmetric borrowing hydrogen catalysis.^[8]

Iridium-based systems, mainly half-sandwich cyclopentadienyl Ir^{III} complexes, are among the most active catalysts in the field of catalytic (transfer) hydrogenation chemistry.^[9] The electronic and steric properties of the Cp* (Cp* = η^5 -C₅Me₅) ligand are essential in the high performance of [Cp*IrCl₂]₂ either in hydrogen-transfer oxidation or reduction reactions,^[10] or in N-alkylation of amines with alcohols.^[11] In fact, [Cp*IrCl₂]₂ has been applied for the coupling amines and alcohols in the absence of base,^[9f,12] the N-heterocyclization of primary amines with diols,^[13] or even the N-alkylation of carbohydrate-based amines.^[14] N-Heterocyclic carbenes (NHCs) have attracted considerable attention as ligands for the design of transition-metal catalysts. The distinct stereoelectronic properties of NHCs make them efficient ancillary ligands not only for the stabilization of reactive intermediates but also for the improvement of the catalytic activity. In addition, their tuneable character allows for the control of the sterical and electronic properties at the metal centre that has made possible the design of specific catalysts for a variety of catalytic transformations including transfer hydrogenation and hydrogen autotransfer reactions.^[15]

presence of a functional group of poor coordination ability on the catalyst structure enhances the transfer hydrogenation activity.^[19,20,21,22] In fact, we have found an interesting relationship between the donor function, the flexibility of the backbone and the length of the linker with the catalytic activity in transfer hydrogenation in a series of rhodium and iridium(I) complexes containing NHC ligands featuring O- and N- donor functions.^[23]

Our current research interest is focused on the synthesis and catalytic applications of transition metal complexes containing heteroditopic ligands of hemilabile character. We have recently reported the catalytic activity of [IrX(cod)(Melm \cap Z)] (\cap Z functionalised wingtip) complexes in the β -alkylation of secondary alcohols with primary alcohols.^[24] Interestingly, experimental and theoretical mechanistic studies support the participation of the iridium catalyst not only in the dehydrogenation and hydrogenation steps but also in the cross-condensation key step leading to the formation of the new C-C bond. Iridium catalytic systems based on [Ir(μ -Cl)(cod)]₂ in combination with functionalised P,N-ligands^[4c,25] or benzoxazolyl iridium(III) complexes^[26] have also shown good catalytic activity in borrowing hydrogen for C-C or C-N bond forming reactions at low catalyst loadings and milder reaction conditions. Taking these results into account, the aim of this work is to evaluate the potential of selected Ir^I(cod) complexes catalyst precursors having a heteroditopic NHC ligands developed by us in the N-alkylation of amines applying the borrowing hydrogen methodology.

On the other hand, most mechanistic proposals for the catalysed N-alkylation of amines with alcohols assume that the aldehyde-amine condensation step takes place outside the coordination sphere of the catalyst. Mechanistic studies supported by DFT calculations are rather scarce and generally focused on catalytic systems based on the Cp*Ir^{III} motif such as those reported by the groups of Eisentein and Crabtree,^[27] Madsen and Fristrup^[28] and recently, by Martín-Matute^[29] and Liu.^[30] Thus, an additional motivation for us is the study of the overall reaction mechanism from a combined experimental and theoretical approach in order to ascertain the role of the catalyst in the aldehyde-amine condensation leading to the imine intermediate product.

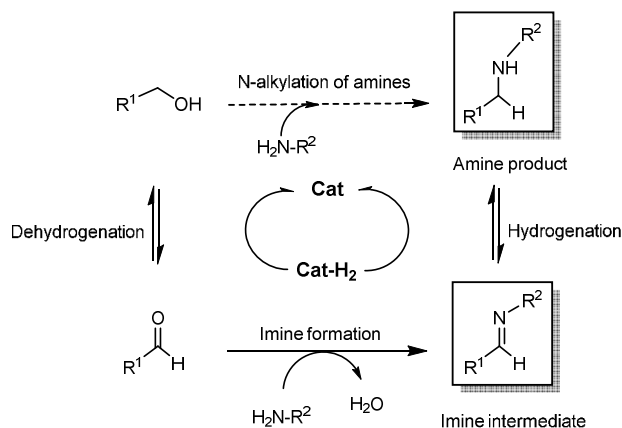


Chart 1. Borrowing hydrogen mechanism for C-N bond formation in the amination of alcohols (Cat-H₂ denotes the formal abstraction of two hydrogen atoms by the catalyst).

NHC ligands have been increasingly used in the design of hydrogen transfer catalysts. In this context, modified Cp*Ir^{III} catalysts having Cp*-tethered NHC ligands,^[16] or bidentate pyrimidine-,^[17] hydroxy-, ether- and alkoxide-functionalised^[9f,18,19] NHC ligands, have allowed to improve the catalytic activity, with regard to that of [Cp*IrCl₂]₂, in several C-C and C-N bond-forming processes through the borrowing hydrogen catalysis. NHC-Ir^I complexes featuring a diene ligand also exhibit a high catalytic performance in hydrogen transfer reactions. It has been reported that the

2. Experimental

Scientific Equipment

¹H NMR spectra were recorded on a Bruker Avance 300 (300.1276 MHz and 75.4792 MHz) or Bruker Avance 400 (400.1625 MHz and 100.6127 MHz) spectrometers. The catalytic reactions were analysed on an Agilent 4890 D system equipped with an HP-INNOWax capillary column (0.4 μ m film thickness, 25 m x 0.2 mm i. d.) using mesitylene as internal standard. Organic compounds were identified by Gas Chromatography-Mass Spectrometry (GC/MS) using an Agilent 6890 GC system with an Agilent 5973 MS detector,

equipped with a polar capillary column HP-5MS (0.25 μ m film thickness, 30 m x 0.25 mm i. d.).

Catalyst synthesis

The neutral iridium(I) complexes [IrX(cod)(Melm \cap Z)] (**1**, X = Br, \cap Z = 2-methoxybenzyl; **2**, X = Cl, \cap Z = 3-dimethylaminopropyl) were straightforwardly prepared by reaction of the corresponding functionalised imidazolium salts with the dinuclear complex [Ir(μ -OMe)(cod)]₂ following the procedure previously reported. The cationic complex [Ir(NCCH₃)(cod){Melm(2-methoxybenzyl)}][BF₄] (**3**) was prepared by abstraction of the bromido ligand in **1** by AgBF₄ in the presence of acetonitrile. Complex [Ir(cod){Melm(pyridin-2-ylmethyl)}][BF₄] (**4**) was prepared by reaction of the NHC–silver complex with the solvate complex [Ir(cod)(OCMe₂)₂][BF₄].^[23b]

General procedure for the N-alkylation of amines with alcohols

The catalytic N-alkylation reactions were carried out under an argon atmosphere in thick glass reaction tubes fitted with a greaseless high-vacuum stopcock. In a typical experiment, the reactor was charged with a solution of the amine (3.0 mmol) and the alcohol (3.0 mmol) in toluene (0.3 mL), internal standard (mesitylene, 70 μ L, 0.5 mmol), base (KOt-Bu, 1.5 mmol) and the catalyst (0.03 mmol, 1 mol%). The resulting mixture was stirred at room temperature until complete dissolution of the catalyst and then placed in a thermostat oil bath at 110 °C. Conversions were determined by gas chromatography analysis (GC) through the following procedure. At different time intervals, 0.1 mL aliquots were taken out of the reaction mixture and quenched in a stirred flask containing water (1 mL) and diethyl ether (1 mL). The organic phase was separated and analysed by GC under the following conditions: column temperature 80 °C (2 min) to 220 °C at 15 °C/min at flow rate of 1 mL/min using ultra pure He as carrier gas, and temperatures of 300 °C for the injector and the fid detector.

General procedure for the isolation of the N-alkylated amine products

Following the general procedure for the catalysed N-alkylation of amines with alcohols, once the reaction is finished, the reaction mixture was cooled to room temperature and all volatiles removed under vacuum. Water (5 mL) was added to the residue and extracted with diethyl ether (3x10 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent removed under vacuum. The residue was dissolved with 3 mL hexane and then eluted through a silica gel column using hexane/diethyl ether (typically 5:1) as eluent. NMR data for the N-alkylated amine products are given in the Supporting Information.

Monitoring of the N-alkylation of aniline with benzyl alcohol catalysed by complex 6

An NMR tube was charged with catalyst [Ir(NCCH₃)(cod){Melm(2-methoxybenzyl)}][BF₄] (**6**) (16.4 mg, 0.030 mmol) and KOt-Bu (16.8 mg, 0.30 mmol) in [D₈]toluene

(0.4 mL). Then, aniline (27 μ L, 0.30 mmol) and benzylalcohol (31 μ L, 0.30 mmol) were added sequentially and the reaction progress monitored by NMR at 80 °C. The conversion of benzylalcohol and the selectivity to N-benzylaniline and N-benzylideneaniline was determined by integration of selected resonances in the ¹H NMR spectrum.

Calculation details

DFT calculations have been carried out with Gaussian 09^[31] using the B3PW91 functional with a 6-31G** basis set for all atoms but Ir, where the LANL2DZ basis set and pseudopotential has been used supplemented with an additional f function. Solvent effects in toluene have been included.^[32] All the minima have been characterized by frequency calculation. Additionally the transition structures have been checked by examining visually the imaginary frequency and by IRC calculations. The structures in Figures 4 and 5 have been depicted using CYLview, 1.0b.^[33]

3. Results and discussion

The Catalysts.

Neutral iridium(I) complexes of formula [IrX(cod)(Melm \cap Z)] (**1**, X = Br, \cap Z = 2-methoxybenzyl and **2**, X = Cl, \cap Z = 3-dimethylaminopropyl)^[23b] were prepared by deprotonation of the corresponding imidazolium salts with the methoxo ligands in the dinuclear complex [Ir(μ -OMe)(cod)]₂.^[34] Compound **1** is a suitable precursor for the preparation of the cationic complex [Ir(cod){Melm(2-methoxybenzyl)}(NCCH₃)]⁺[BF₄][−] (**3**) by abstraction of the bromido ligand by AgBF₄ in the presence of acetonitrile. In contrast, the higher coordination ability of the pyridine donor set allows for the synthesis of complex [Ir(cod){Melm(pyridin-2-ylmethyl)}][BF₄] (**4**) from [IrBr(cod){Melm(pyridin-2-ylmethyl)}] following this procedure (Chart 2). However, the more convenient synthesis of this complex relies on the NHC transfer from the silver complexes [AgX(NHC)]_x, generated in situ, to the cyclooctadiene solvato [Ir(cod)(OCMe₂)₂]⁺ species containing labile acetone ligands.^[23b]

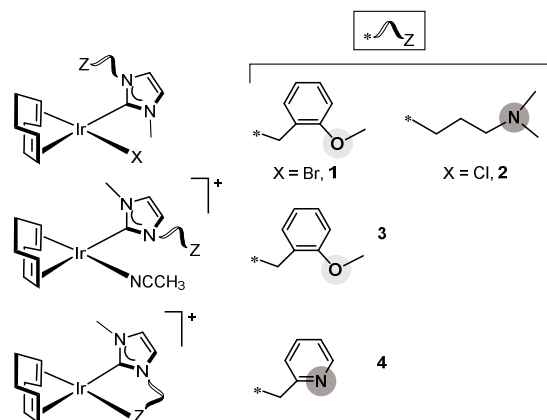


Chart 2. Neutral and cationic iridium(I) complexes with functionalised NHC ligands as catalysts for N-alkylation of amines with alcohols.

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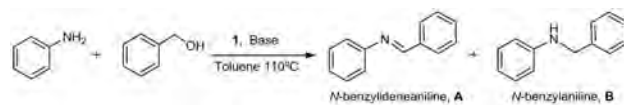
The iridium(I) complexes featuring Melm \cap Z ligands have shown excellent catalytic activity in transfer hydrogenation of several unsaturated substrates as ketones, aldehydes, α,β -unsaturated ketones and imines using 2-propanol as hydrogen source. A comparative study has shown that cationic complexes are more efficient than neutral ones, and also that complexes having O-functionalised NHC ligands provide much more active systems than those having NHC ligands with N-donor functions with TOFs up to 4600 h⁻¹ for the transfer hydrogenation of cyclohexanone in 2-propanol/KOH medium.^[23b]

These iridium(I) complexes are also moderately active in the oxidation of primary and secondary alcohols in Oppenauer-type oxidation processes, and in the tandem reaction of β -alkylation of secondary alcohols with primary alcohols in the presence of base. Catalyst precursors **1** and **3**, both with a NHC ligand with a 2-methoxybenzyl wingtip, were found to be the most active in this series. In particular, the cationic complex **3** showed the best catalyst performance in the dehydrogenation of benzyl alcohol in acetone, with an initial TOF₀ of 1283 h⁻¹, and also in the β -alkylation of 2-propanol with butan-1-ol with a 94 % of conversion in 10 h and complete selectivity for heptan-2-ol.^[24] A preliminary screening of these catalysts in the N-alkylation of amines also evidenced the superior catalytic performance of complexes **1** and **3**. However, the potential of catalysts **2** and **4** having N-functionalised NHC ligands was also identified.

N-Alkylation of Amines with Alcohols Catalysed by Iridium Complexes with O/N-donor functionalised NHC Ligands.

In order to determine the ability of our catalysts for the N-alkylation of amines, the coupling of aniline with benzyl alcohol was selected as model reaction under the reaction conditions optimized by Fujita *et al.* for the catalytic system based on [Cp*IrCl₂]₂.^[10,13] Complex [IrBr(cod){Melm(2-methoxybenzyl)}] (**1**) was chosen for the catalytic tests due to its high catalytic activity in transfer hydrogenation reactions and better accessibility from a synthetic point of view. The reactions were conducted using a catalyst loading of 1 mol% for 5 h in toluene (0.3 mL) and equimolar amounts of both substrates (3 mmol). First, various organic and inorganic bases were examined in order to determine the best reaction conditions (Table 1). No reaction was found in the absence of catalyst using Cs₂CO₃ as base (entry 1). Although Cs₂CO₃, KOH and NaOMe provided conversions of about 80 % with a catalyst/base/amine ratio of 1:50:100 (entries 2-4), KOt-Bu has shown to be the best base giving almost quantitated conversion with a selectivity for the N-benzylaniline product as high as 98 % (entry 5). The reduction of the amount base resulted in a decrease of both the catalytic activity and amine selectivity (entries 6 and 7).

Table 1. Base screening for the N-alkylation of aniline with benzyl alcohol catalysed by [IrBr(cod){Melm(2-methoxybenzyl)}] (**1**).^{a,b}



Entry	Catalyst	Base	Catalyst:base:aniline	Conv. (%)	A / B ratio
1	None	Cs ₂ CO ₃	1:50:100	0	- / -
2	1	Cs ₂ CO ₃	1:50:100	82	18 / 82
3	1	KOH	1:50:100	81	7 / 93
4	1	NaOMe	1:50:100	79	15 / 85
5	1	KOt-Bu	1:50:100	99	2 / 98
6	1		1:40:100	81	18 / 82
7	1		1:25:100	68	29 / 71

[a] Reaction conditions: catalyst (0.03 mmol, 1 mol%), benzyl alcohol (3 mmol), aniline (3 mmol) and base, in toluene (0.3 mL) at 110 °C for 5 h. ^b Determined by GC based on the benzyl alcohol using mesitylene as internal standard.

The catalytic activity in N-alkylation reactions of selected iridium complexes having O/N-donor functionalised NHC ligands has been evaluated in the alkylation of aniline with benzyl alcohol under the base-optimized reaction conditions determined for catalyst **1**, catalyst/KOt-Bu/amine ratio of 1:50:100 (Table 2). Conversions of benzyl alcohol higher than 90 % in 2 h were attained with the neutral catalyst precursors **1** and **2** and the cationic compound **4** (entries 1, 3 and 6). However, the same level conversion was reached with catalyst **3** in only 1 h (entry 4) although with poor selectivity for the amine product. The selectivity is strongly dependent on the reaction time. It has been found that longer reaction times result in almost complete selectivity for the amine reaction product (entries 2, 5, and 7), which is in line with previous observations for related catalytic systems.³⁵ Likely, either imine coordination or the hydrogenation of the intermediate imine product could be the slow step in the global tandem reaction. In fact, the reaction profile of the N-alkylation of aniline with benzyl alcohol shows the accumulation of the intermediate imine at the initial stage of the reaction, which is consumed as the reaction proceeds (Figure 1). The most efficient catalyst precursor is the cationic complex [Ir(NCCH₃)(cod){Melm(2-methoxybenzyl)}][BF₄] (**3**) that gave quantitative conversion in 3 h with complete selectivity to N-benzylaniline (entry 5). Interestingly, similar results were obtained with catalysts **1** and **4** after 5 h (entries 2 and 7).

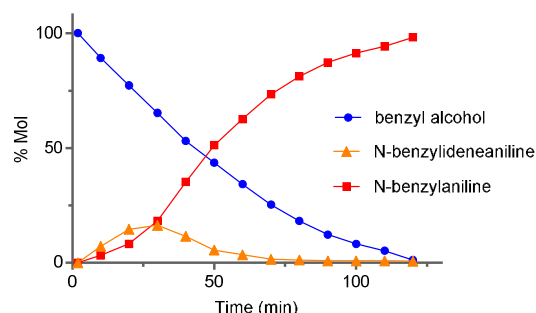


Figure 1. Time dependence of the N-alkylation of aniline with benzylalcohol catalysed by **3** (10 mol%) in $[D_8]$ toluene at 80 °C monitored by 1H NMR.

In order to study the influence of the donor function on the NHC ligand in the performance of our iridium catalysts, the catalytic activity of related iridium(I) compounds $[IrCl(cod)(Ime)]$ (**5**) ($Ime = 1,3$ -dimethylimidazol-2-ylidene)^[36] and $[IrCl(cod)(IPr)]$ (**6**) ($IPr = 1,3$ -bis(2,6-diisopropylphenyl)imidazol-2-ylidene),^[37] having small and bulky unfunctionalised NHC ligands respectively, has been investigated. As we can observe in Table 2, the catalytic activity of both complexes is notably inferior giving a 69 % and 21 % conversion in 4 h (entries 8 and 10). However, full conversion was attained with catalyst **5** in 8 h giving a 97% of selectivity for the higher amine product (entry 9). The cyclooctadiene iridium chlorido dimer **7**, lacking an NHC ligand, has a negligible catalytic activity (entry 11). Finally, the reference system $[Cp^*IrCl_2]_2$ (**8**) is also much less active (entry 12) which highlights the positive influence of the O/N-donor function on the catalyst structure.

With the aim of determine the substrate scope, aniline was alkylated with a range of primary and secondary alcohols using the most active iridium catalysts **1**, **3** or **4** under the optimized reaction conditions of 1 mol% of catalyst in toluene at 110 °C and $KOt-Bu$ as base. As can be seen in Table 3, N-alkylation of aniline with *para*-substituted benzyl alcohols proceeds efficiently with catalysts **1** and **3**, regardless of the electronic character of the substituent (entries 3-6). The corresponding N-benzylaniline product was selectively obtained in only 3 h with catalyst precursor **3** independently of the used alcohol, benzyl alcohol (entry 2), (4-methoxyphenyl)methanol, (entry 4) or (4-bromophenyl)methanol (entry 6).

Straight chain alcohols have also been used as alkylating agents for the preparation of a range of N-alkylaniline derivatives although longer reaction times are required. Thus, catalyst precursor **1** efficiently catalysed the alkylation of aniline with butan-1-ol or hexan-1-ol affording quantitatively the corresponding N-alkylaniline in 6 h (entries 8 and 9). In the same way, 2-phenyletan-1-ol and 4-phenylbutan-1-ol were transformed into N-phenethyl/phenylbutyl-aniline in 7 and 3.5 h (entries 10 and 11). It is worth noting that shorter reaction times resulted in good alcohol conversions although with moderate selectivity for the amine product (entries 7 and 11).

Table 2. Catalyst screening for the N-alkylation of aniline with benzyl alcohol catalysed by iridium(I) complexes having O/N-donor-functionalised NHC ligands.^{a,b}

Entry	Catalyst	t (h)	conv. (%) ^b	A/ B ratio	
1		2	93	7 / 93	
2		5	99	2 / 98	
3		2	94	5 / 95	
4		1	94	23 / 77	
5		3	99	1 / 99	
6		2.3	92	4 / 96	
7		5	97	1 / 99	
8		4	69	21/79	
9		8	99	3/97	
10		6	21	37 / 63	
11	$[Ir(\mu-Cl)(cod)]_2$ ²⁵	7	24	34	
12	$[Cp^*IrCl_2]_2$ ^{13d}	8	17	94	

[a] Reaction conditions: catalyst (0.03 mmol, 1 mol%), benzyl alcohol (3 mmol), aniline (3 mmol) and $KOt-Bu$ (1.5 mmol) in toluene (0.3 mL) at 110 °C. [b] Determined by GC analysis based on the secondary alcohol using mesitylene as internal standard. [c] A/B ratio not reported in the literature.

The alkylation of aniline with secondary alcohols was also investigated. Good conversions were attained in the reaction of aniline with 1-phenylethanol catalysed by **1** or **3** in 3 h although roughly an equimolecular mixture of the corresponding imine and amine products was obtained (entries 12 and 13). Interestingly, catalyst $[Ir(cod)\{MeIm(pyridine-2-ylmethyl)\}][BF_4]$ (**4**) gave 78 % of selectivity for the N-(1-phenylethyl)aniline product after 4 h (entry 14). Thus, 4-phenylbutan-2-ol was quantitatively transformed into N-(4-phenylbutan-2-yl)aniline in 5 h using catalyst precursor **4** (entry 17). These results suggest that the more sterically encumbered secondary ketimines are harder to reduce than the corresponding secondary aldimines by the Ir^I -NHC catalysts which is in agreement with that observed by Fujita *et al.* with the catalytic system based on $[Cp^*IrCl_2]_2$.^[13] However, this trend is not followed by catalyst $[Cp^*Ir(NH_3)_3][X]$ ($X = Cl, Br$).^[38]

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Table 3. N-alkylation of aniline with alcohols catalysed by iridium(III) complexes having O/N-donor-functionalised NHC ligands.^{a,b}

Entry	Amine	Alcohol	Catalyst	t (h)	conv. (%)	A/B ratio ^c
1			1	5	99	2/98 (92%)
2			3	3	99	1/99
3			1	2	93	8/92
4			3	3	99	1/99
5			1	2	94	7/93
6			3	3	99	2/98
7			1	4	93	13/87
8			1	6	99	1/99
9			1	6	99	1/99 (97%)
10			1	7	99	9/91 (84%)
11			1	3.5	94	14/86
12			1	3	95	58/42
13			3	3	94	55/45
14			4	4	95	22/78
15			1	3	96	57/43
16			4	4	98	15/85
17			4	5	99	1/99

[a] Reaction conditions: catalyst (0.03 mmol, 1 mol%), alcohol (3 mmol), aniline (3 mmol) and KOt-Bu (1.5 mmol) in toluene (0.3 mL) at 110 °C. [b] Determined by GC analysis based on the alcohol using mesitylene as internal standard. [c] Isolated yield in parenthesis.

The substrate scope was expanded by using a range of aliphatic and aromatic amines including *p*-toluidine, 2-methoxyaniline, benzylamine and 2-phenylethanamine (Table 4). *p*-Toluidine was successfully alkylated with benzyl alcohols with catalysts **1** and **3** with excellent conversions and selectivities in 2–3 h (entries 1–4). Butan-1-ol and 2-phenylethan-1-ol can be used as alkylating reactants although longer reaction times, typically 8 h, are required in order to attain complete selectivity for the corresponding amine products (entries 5–7). Good conversions were observed in the alkylation of 2-methoxyaniline with benzyl alcohols after 2 h using catalyst **1**, albeit with moderate selectivities (entries 8 and 10). Nevertheless, selectivities higher than 95 % for the alkylated amine products were attained at longer reaction times (8–12 h, entries 9 and 11). The more nucleophilic aliphatic amines are substrates harder to alkylate due to the possible blocking of the coordination sites at the catalyst thereby preventing the oxidation of the alcohol.³⁹ The alkylation of benzylamine with benzyl alcohol catalysed by **1** gave 92 % of conversion in 48 h with 97 % selectivity for dibenzylamine (entry 12). In contrast, the alkylation of 2-phenylethanamine with benzyl alcohol proceeds faster with catalysts **1** and **4** giving excellent conversions in 10 h with selectivities for N-benzyl-2-phenylethan-1-amine higher than 90 % (entries 14 and 15).

Alkylated amines from selected catalytic runs giving a high selectivity (Table 3, entries 1, 9 and 10; Table 4, entries 2, 7, 12 and 14) have been isolated as colourless oils in 81–97 % yield after purification by chromatography column (see the Supporting Information).

Table 4. N-alkylation of amines with alcohols catalysed by iridium(III) complexes having O/N-donor-functionalised NHC ligands.^{a,b}

Entry	Amine	Alcohol	Catalyst	t (h)	conv. (%)	A/B ratio ^c
1			1	2	95	6/94
2			3	3	94	1/99 (83%)
3			1	2	94	6/94
4			3	3	99	1/99
5			1	4	92	15/85
6			3	8	99	1/99
7			1	8	92	1/99 (83%)
8			1	2	94	20/80
9			1	8	97	5/95
10			1	2	93	29/71
11			1	12	98	2/98
12			1	48	92	3/97 (81%)
13			1	6	72	65/35
14			1	10	92	9/91 (91%)
15			4	10	93	8/92

[a] Reaction conditions: catalyst (0.03 mmol, 1 mol%), alcohol (3 mmol), aniline (3 mmol) and KOt-Bu (1.5 mmol) in toluene (0.3 mL) at 110 °C. [b] Determined by GC analysis based on the alcohol using mesitylene as internal standard. [c] Isolated yield in parenthesis.

Mechanistic Studies.

The N-alkylation of amines with alcohols is a tandem reaction that proceeds via successive hydrogen transfer oxidation of primary or secondary alcohols (borrowing hydrogen) to give an aldehyde or ketone, respectively, followed by amine condensation mediated by base to afford an imine (and water) which is reduced by transfer hydrogenation to the amine (Chart 1).^[2] In order to explore the possible participation of the iridium catalyst in the amine-carbonyl compound condensation step leading to the new C–N bond, the reaction of aniline with benzaldehyde has been studied in detail. In the presence of 1 mol% of catalyst **1** complete conversion to N-benzylideneaniline was observed in only 5 min at 110 °C or 30 min at room temperature (50 % of KOt-Bu in 0.3 mL of toluene). However, in the absence of catalyst a 93 % was formed in 30 min at 110 °C or in 12 h at room temperature. This result suggests that the condensation process is taking place on the coordination sphere of the iridium centre.

In this context, it is worth mentioning that DFT calculations support the participation of Ir(I)-NHC catalysts in the cross-aldol condensation reaction, the key step leading to the formation of the new C-C bond in the β -alkylation of secondary alcohols with primary alcohols.²⁴ On the other hand, the positive effect of a donor function in Ir(I)-NHC catalysts in hydrogen transfer oxidation and reduction catalytic reactions has also been identified.^[19,20,21,23b,29]

It is known that catalytic systems based on $[\text{Ir}(\mu\text{-OMe})(\text{cod})]_2$ in combination with functionalised phosphano ligands such as $\text{Py}_2\text{NPiPr}_2$, N-phosphanopyridin-2-amine,^[40] or dppf (1,1-bis(diphenylphosphanoferrocene))^[41] are efficient not only for the monoalkylation of aromatic amines, but also for heteroaromatic substrates such as aminopyridines, which are usually more difficult to alkylate,^[40] or more elaborated aromatic amines as tryptamine derivatives.^[41] We have performed N-alkylation catalytic experiments using $1/\text{PPh}_3$ or $1/\text{dppe}$ (diphenylphosphanoethane) as catalytic systems. A drastic reduction on the activity was observed in the case of PPh_3 and the complete inhibition of the catalytic activity in the presence of dppe . In addition, the ^1H NMR spectra of solutions of compounds **1** or **3** in $[\text{D}_6]$ acetone recorded after the addition of dppe showed the presence of free 1,5-cyclooctadiene. These results suggest that the diene and NHC ligands might be present in the coordination sphere of the catalytic active species.

On the basis of the experimental observations, the proposed mechanism for the N-alkylation of amines with alcohols catalysed by iridium(I) complexes having functionalised NHC ligands is depicted in Figure 2. The mechanism is composed of two processes, in a first stage the

imine is formed through a condensation of an aldehyde/ketone with the amine, and in the second one, the generated imine is hydrogenated to the final amine product. Under this framework, the alkoxo species $[\text{Ir}(\text{cod})(\text{Melm}\cap\text{Z})(\text{OR})]$ takes part in both catalytic cycles. Firstly, β -hydride elimination (step i) result in the formation of the corresponding aldehyde partner and the hydrido species $[\text{IrH}(\text{cod})(\text{Melm}\cap\text{Z})]$ that is responsible for the reduction of the intermediate imine product through consecutive imine coordination, insertion into the Ir-H bond, and alcoholysis (steps ii-iv, imine hydrogenation cycle). On the other hand, the participation of an amido intermediate is proposed in the formation of the intermediate imine product (imine formation cycle). Thus, reaction of the alkoxo complex with the amine might result in the formation of an intermediate amido species (step i). Nucleophilic attack of the amido ligand on the carbon atom of the electrophilic aldehyde could lead to the hemiaminol intermediate species (step ii) that is released by alcoholysis with regeneration of the key alkoxo species (step iii). Finally, the free hemiaminal dehydrates to give the corresponding imine in a process that is favoured by the high temperature at which the catalytic process takes place.^[42] The proposed mechanism involves a Ir-H monohydride intermediate as the competent catalytic species for the hydrogenation of the imine product which is in agreement with the deuteration studies carried out on triazolyldene iridium complexes¹⁹ and our previous mechanistic studies on related NHC-Ir^(I) complexes.²³

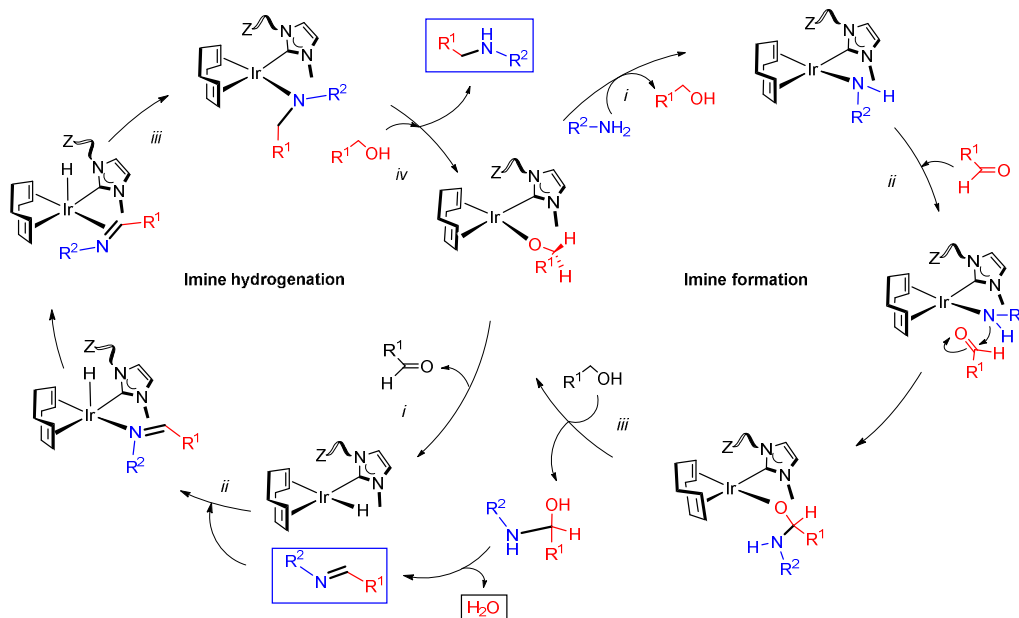


Figure 2. Proposed mechanism for the N-alkylation of amines with alcohols catalysed by iridium(I) complexes having functionalised NHC ligands comprising two independent catalytic cycles: imine formation and imine hydrogenation.

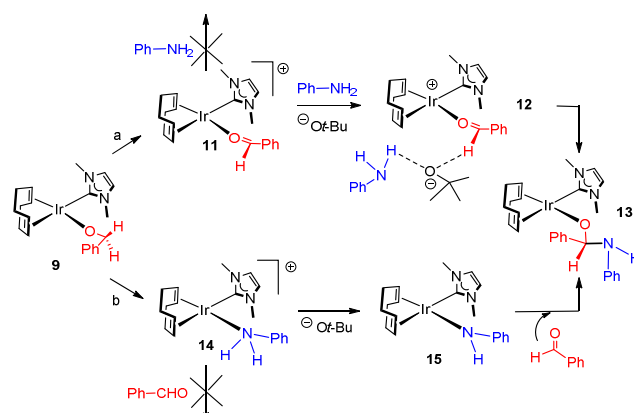
In order to support the proposed mechanism, the N-alkylation of aniline with benzyl alcohol has been computationally studied at DFT level. In the following discussion all the energies are reported in terms of ΔG (kcal/mol). In the global reaction yielding an amine thorough a condensation process between benzaldehyde and aniline to give an imine that is eventually hydrogenated, one of the processes involved must be the oxidation of benzyl alcohol to benzaldehyde. Our experimental results suggest that the cod ligand remains coordinated and that imine formation is much faster in the presence of the catalysts. Under these assumptions we have devised a catalytic cycle involving a catalyst that keep the “Ir(cod)(NHC)” moiety intact. In the following DFT calculations we have used a model system where NHC is the simple IMe, 1,3-dimethyl-imidazol-2-ylidene. Therefore, in the basic medium where this reaction takes places the first step is the activation of [IrCl(cod)(IMe)] (**5**) to [Ir(cod)(IMe)(OCH₂Ph)] (**9**) which is an exergonic process ($\Delta G = -21.60$ kcal/mol). We assume that **9** is the catalytically active species because it can be formed spontaneously from **5** and then, it will be taken as the energy reference for the following discussion.

Complex [Ir(cod)(IMe)(OCH₂Ph)] (**9**), via a β -H elimination process through **TS₉₋₁₀**, gives benzaldehyde and the hydride species [IrH(cod)(IMe)] (**10**) ($\Delta G = 0.92$ kcal/mol) which will be consumed later at the imine hydrogenation and amine-aldehyde condensation processes, respectively. The β -H elimination process through **TS₉₋₁₀** requires an activation energy of 25.54 kcal/mol (Figure 3). The H transferred from the benzyloxy ligand to the metal in transition state **TS₉₋₁₀** is at 1.70 and 1.59 Å from the iridium atom and the original carbon atom, respectively. In the final complex [IrH(cod)(IMe)] (**10**) the Ir-H distance takes an eventual value of 1.64 Å.

Once benzaldehyde is formed, two different pathways could be devised where either the aldehyde or the amine replaces the benzyloxy ligand in [Ir(cod)(IMe)(OCH₂Ph)] (**9**) (Scheme 1). The attack of an external amine molecule on coordinated aldehyde or alternatively, the attack of aldehyde on coordinate amine could lead to formation of the same hemiaminal molecule. As we will show, both pathways are unlikely as such a simple process (see Supporting Information) and the reaction eventually requires coordination of the amine as an amido ligand formed by deprotonation of aniline.

In the first pathway, Scheme 1a, the coordination of benzaldehyde in replacement of the benzyloxy ligand in [Ir(cod)(IMe)(OCH₂Ph)] (**9**) to give [Ir(cod)(IMe)(O=CHPh)] (**11**) is noticeably endergonic ($\Delta G = +74.60$ kcal/mol). Inasmuch, the scan of the reaction path corresponding to a nucleophilic attack of the amine onto a coordinated aldehyde has been found to be an uphill process and no TS has been found. This is, probably, a consequence of the quaternization of the nitrogen atom. The quaternary nature of the amino nitrogen atom after the nucleophilic attack could be alleviated by

influence of the basic environment, which would allow for deprotonation of the quaternary nitrogen atom.



Scheme 1. Alternative mechanisms for the imine formation catalysed by [Ir(cod)(IMe)(OCH₂Ph)] (**9**).

We have studied the mechanism of the nucleophilic attack of the amine on the carbon atom of a coordinated benzaldehyde in the presence of a hydrogen-bonded *tert*-butoxide anion. This has led to the location of a transition state, **TS₁₂₋₁₃**, which shows a forming C-N bond while, simultaneously, a proton is transferred from the aniline molecule to the *tert*-butoxide anion (See Supporting Information). An IRC calculation on the **TS₁₂₋₁₃** followed by full optimization of the extrema found was carried out. On the reactant side of the path, coordinated benzaldehyde, we have located an ionic pair **12** formed by the unit **11**, a ⁻O⁻t-Bu anion and the incoming aniline molecule. The ⁻O⁻t-Bu anion sits between the benzaldehyde in **11** and is hydrogen bonded to the CH group of the benzaldehyde ligand and to the amine group of the aniline molecule. This ionic pair has an energy of $\Delta G = -37.5$ kcal/ relative to the independent **11**, ⁻O⁻t-Bu and aniline units and +37.1 kcal/mol relative to the starting reference compound [Ir(cod)(IMe)(OCH₂Ph)] (**9**). The transition state found leading to an O-bonded hemiaminolato complex [Ir(cod)(IMe)(O-CHPhNHPh)] (**13**) and a molecule of *t*-BuOH, **TS₁₂₋₁₃**, is just 2.8 kcal/mol above the ion pair **12**.

After reaction with benzyl alcohol a hemiaminal molecule is released from **13**, and the resulting alkoxo complex [Ir(cod)(IMe)(OCH₂Ph)] (**9**) returns to the catalytic cycle. The hemiaminal then dehydrates leading to the imine, which will be later hydrogenated. Although the activation energy for this pathway, once formed the ion pair **12**, is energetically feasible, it would require the prior coordination of benzaldehyde in place of the benzyloxy ligand before it could be completed. As we have shown this is highly endergonic process, which makes this pathway unsuitable for the catalytic process.

Most theoretical studies^{29,30,43,44} on catalysed N-alkylation assume that the aldehyde-amine condensation occurs outside the coordination sphere of the catalyst whose role involves

just the hydrogen transfer steps, namely oxidation of the alcohol to aldehyde and then hydrogenation of the imine formed by condensation of aldehyde and amine. On the other hand, studies by Fujita *et al.*^{13a} and mechanistic/theoretical studies of Fristrup and Madsen²⁸ on the catalytic activity of $[\text{Cp}^*\text{IrCl}_2]_2$, found that the condensation process takes place within the coordination sphere of the iridium centre and the imine product is formed and reduced without leaving the coordination sphere of the catalyst. In addition, the role of

pincer ruthenium catalysts in coupling reaction of amines with alcohols has also been studied.^{45,46} According to our experimental results, the N-alkylation process proceeds within the coordination sphere of the catalyst but, in contrast to the Fristrup and Madsen results,²⁸ the build-up of free imine is observed probably because hemiaminal is released and then dehydrated to imine outside the coordination sphere of the active species before it is hydrogenated.

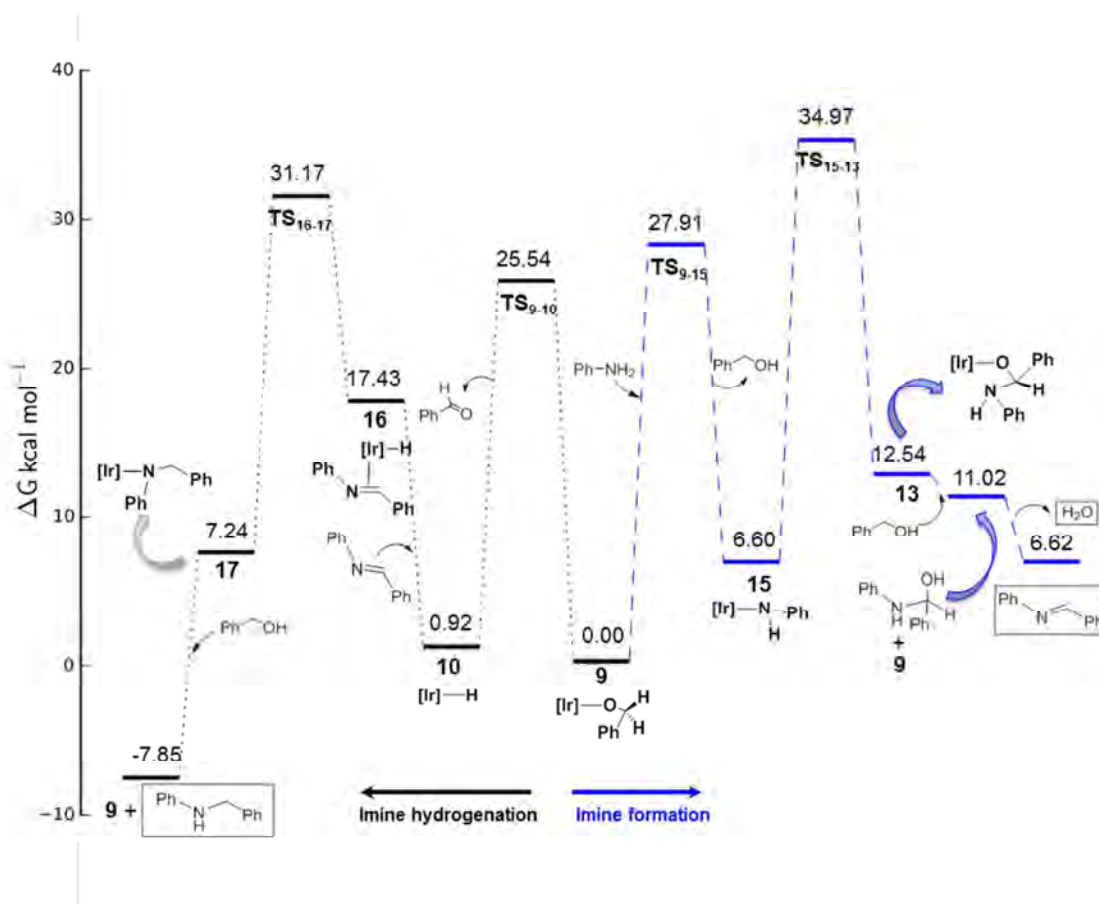


Figure 3. DFT calculated relative energy profile (ΔG in kcal/mol) for imine formation through an anilido ligand and imine hydrogenation by a transfer hydrogenation pathway.

An alternative reaction path, Scheme 1b, can be devised via amine coordination. As shown before for benzaldehyde, direct coordination of aniline in replacement of the benzyloxide ligand in $[\text{Ir}(\text{cod})(\text{Ime})(\text{OCH}_2\text{Ph})]$ (**9**) to give $[\text{Ir}(\text{cod})(\text{Ime})(\text{NH}_2\text{Ph})]$ (**14**) is also noticeably endergonic ($\Delta G = +72.50$ kcal/mol). On the other hand, a direct attack of an aldehyde molecule to the amine ligand is highly unlikely because of the bond saturation and the absence of a lone electron pair on the coordinated nitrogen donor atom and preliminary calculations have shown that it is an uphill route. In most studies the imine formation step is not modelled as it is taken as a standard reaction outside the coordination sphere

of the catalyst but in a basic environment the amine could be actually coordinated as an amido ligand. An amido ligand could supply a lone pair available to an eventual nucleophilic attack to an external aldehyde molecule. The increased acidity of coordinated vs. free amines is well documented⁴⁷ and, on the other hand, the capability of alkoxo ligands to deprotonate amines⁴⁸ or ammonia⁴⁹ is also well known.

Otherwise, substitution of the benzyloxide ligand in **9** by an anilido ligand to give $[\text{Ir}(\text{cod})(\text{Ime})(\text{NHPh})]$ (**15**) is just slightly endergonic ($\Delta G = +6.6$ kcal/mol, Figure 3). Nevertheless, the high endergonicity of the direct substitution of benzyloxide by aniline suggests that the formation of the anilido ligand must

be either previous (from anilido anion in solution, whose concentration is expected to be negligible) or simultaneous to the substitution process. Following this idea we have studied the entrance of aniline into the coordination sphere of the iridium centre. The transition structure **TS₉₋₁₅** (Figure 4) corresponding to a proton transfer from aniline to benzyloxide has been located which corresponds to an activation energy of $\Delta G = +27.91$ kcal/mol (Figure 3). The transferred proton is located at a distance 1.14 Å of the N of aniline (1.01 Å in free aniline) and 1.37 Å of the O the benzyloxide (0.96 Å in free benzyl alcohol). The Ir-O is 2.54 Å from 1.99 Å in [Ir(cod)(IMe)(OCH₂Ph)] (**9**) and the Ir-N is 2.29 Å and goes to 2.03 Å in the eventual [Ir(cod)(IMe)(NHPh)] (**15**). These data show a late TS where Ir-O bond has elongated substantially and the O-H is not still formed while the formation of the Ir-N bond is quite advanced and the N-H bond is just partially broken.

The lone pair on the amido ligand is a good nucleophile towards the carbonyl carbon atom on benzaldehyde. After reaction of benzaldehyde with **15** the hemiaminolite compound [Ir(cod)(IMe)(O-CHPhNHPh)] (**13**) is formed ($\Delta G = +5.94$ kcal/mol). This process requires an activation energy of $\Delta G^\ddagger = +28.37$ kcal/mol, Figure 3). The N and O donor atoms are virtually chelating the metal atom in **TS₁₅₋₁₃** (Figure 5), the Ir-N distance is 2.21 Å (from 2.03 Å) although the Ir-O distance 2.92 Å is markedly long. The C-O distance is 1.38 Å (1.22 Å in free benzaldehyde) whereas the C-N distance is 2.47 Å and 1.38 Å in the eventual hemiaminolite species **13**. In the final product, **13**, N and O switch their role as donor atoms. The hemiaminolite ligand is coordinated through the O atom (Ir-O of 2.02 Å) and the N atom has moved out of the coordination sphere of iridium. This ligand, after a proton interchange with a benzyl alcohol molecule, leaves the coordination sphere as hemiaminal and regenerates the benzyloxide complex **9**. The free hemiaminal dehydrates to give the corresponding imine in a process which is alcohol mediated in solution.^[45,50]

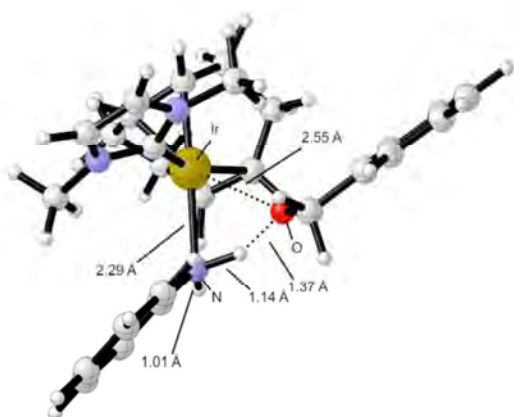


Figure 4. DFT calculated structure of **TS₉₋₁₅** in the process of replacement of a benzyloxide ligand for an anilido ligand.

The condensation reaction is a standard organic reaction that can take place outside the coordination sphere of the catalyst in an alcohol-mediated process.^[44,45,51] We have

modelled the condensation of aniline and benzaldehyde using benzyl alcohol as mediator. The activation energy for the formation of hemiaminal from the separate benzyl alcohol, aniline and benzaldehyde results in $\Delta G^\ddagger = +29.82$ kcal/mol, that is almost 1.5 kcal/mol higher than the transition metal mediated pathway.

As far as we have been able to trace, only Wang *et al.*^[45] and Suresh *et al.*^[46] have considered a possible role of an amido ligand in the way to a hemiaminolite molecule. Wang *et al.* found that the metal mediated hemiaminal formation is close enough in energy to the classic organic condensation reaction to take a role in the reaction, while Suresh *et al.* found that the catalyst-assisted path is more favourable than the simple organic reaction. However, Zhang *et al.*^[44] in a recent paper discard the role of the metal in the condensation step as they found it is not competitive with the classical organic reaction, but they consider only the fully protonated form of the amino ligand. While most studies assume that this reaction takes place outside the coordination sphere of the catalyst, it can be concluded that its possible role cannot be neglected, particularly when it is possible the deprotonation of the amine to an amido ligand, affording a lone pair available as nucleophile towards the aldehyde molecule.

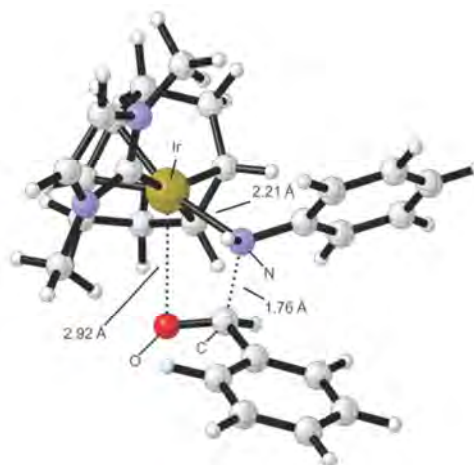


Figure 5. DFT calculated structure of **TS₁₅₋₁₃** in the process of nucleophilic attack of the lone pair of an amido ligand to the electrophile benzaldehyde to form an eventual C-N bond.

The final step is the process of imine hydrogenation which starts by coordination of the imine to the square planar hydrido complex **10**, resulting from β -H elimination in **9**, forming a pentacoordinated square pyramidal intermediate **16** featuring the hydrido ligand in apical positions and a π -bonded imino ligand with the C=N bond parallel to the Ir-H bond and the C-imino atom oriented close to the hydride ligand. An activation energy of 13.74 kcal/mol to **TS₁₆₋₁₇** leads to imine insertion into the Ir-H bond to afford the amido complex **17**. This is followed by alcoholysis and release of the amine reaction product with formation of the starting alkoxo complex **9** (Figure 3 and Supporting Information). In view of the energy spans found for both catalytic cycles (Figure 3, right and left),

the use of a somewhat harsh reaction conditions (refluxing toluene temperature) seems to be necessary.

In order to assess the role of the substituent in the NHC ligand, the highest transition structures in the imine hydrogenation cycle (**TS**₁₆₋₁₇), the C-N bond formation (**TS**₁₅₋₁₃) and the energy reference, compound **9**, have been reoptimized by inclusion of a -C₆H₄OMe substituent (**S-TS**₁₆₋₁₇, **S-TS**₁₅₋₁₃ and **S-9**). Inclusion of the substituent does not change substantially the conclusions obtained by using the model. The substituent group in the NHC ligand does not show any significant interaction with the rest of the complex in any of the structures. In the case of the C-N formation step this has led to two different conformations of the TS (**S-TS**_{15-13-a} and **S-TS**_{15-13-b}) ought to the asymmetry of the NHC ligand which show a difference of 2.5 kcal/mol between them. These transition states lie at 31.5 (**S-TS**_{15-13-a}) and 34.1 (**S-TS**_{15-13-b}) (34.97 in the model). On the other hand, the highest transition state in the imine hydrogenation cycle (**S-TS**₁₇₋₁₈) lie now 30.4 kcal/mol above **S-9** (31.2 in the model). The relative difference between the highest transition states of the imine hydrogenation and C-N formation cycles remain similar. Either the model or the full structures show that the C-N formation step is competitive with the direct condensation of aniline and benzaldehyde and that the role of the catalyst in the imine formation cannot be neglected.

Conclusions

A series of neutral and cationic Ir^I(cod) complexes based on O- and N-donor functionalised NHC ligands (MeImOZ) have shown to be efficient catalyst precursors for the N-alkylation of primary amines with alcohols. The alkylation reactions proceed efficiently not only with the catalysts having a rigid methoxybenzyl wingtip but also with those having N-donor functions in the NHC arm such as pyridin-2-ylmethyl and 3-dimethylaminopropyl. The reactions were conducted in toluene at 1 mol% iridium catalyst loading using KOt-Bu as base to give exclusively the monoalkylation product. The cationic complex [Ir(NCCH₃)(cod){MeIm(2-methoxybenzyl)}]⁺ having a rigid O-donor wingtip exhibited a relatively better catalytic performance for the N-alkylation of aniline with benzyl alcohol. These catalysts have been applied for the alkylation of a variety of aromatic and aliphatic primary amines with a range of alcohols including benzyl alcohol derivatives, straight chain primary alcohols and secondary alcohols. Although good conversions were attained with most substrates at short reaction times, somewhat longer times are required for the selective formation of the corresponding amine product.

The proposed mechanism is based on the experimental findings of the involvement of cod-coordinated species and the evidence of a metal catalysed C-N bond formation step instead of an out-of-cycle condensation reaction. The mechanism comprises two independent catalytic cycles involving the imine formation and the imine hydrogenation. A DFT computational study on the N-alkylation of aniline with benzyl alcohol catalysed by the simpler [IrCl(cod)(IMe)] has

been carried out. With regard to the formation of imine, the calculations shows that either the amine attack onto coordinated aldehyde or direct attack of aldehyde onto a coordinate amine ligand have a large energetically penalty. The C-N formation step requires the involvement of an amido ligand which supplies a lone pair that confers a nucleophile character to the ligand towards aldehyde and makes the C-N formation step feasible. The amido intermediate is formed by deprotonation of the amine substrate during the substitution step of the benzyloxide ligand in the active species [Ir(cod)(IMe)(OCH₂Ph)].

The iridium(I) complexes featuring functionalised NHC ligands are more active than the related complexes [IrCl(cod)(IMe)] and [IrCl(cod)(IPr)] having unfunctionalised NHC ligands and thus, minor energy spans are anticipated. The calculations have shown that the N-alkylation reaction proceeds mainly through square planar intermediates and thus, the coordination of the donor function to the iridium centre could be possible. However, reoptimization of the transition structures for the imine hydrogenation and the C-N bond formation step by inclusion of a 2-methoxybenzyl substituent in the NHC ligand does not show any significant interaction with the rest of the complex. In addition, the relative difference between the highest transition states of the imine hydrogenation and C-N formation cycles remain similar. These results evidence that the role of the iridium catalyst in the C-N formation step of the imine formation catalytic cycle cannot be neglected. The positive influence of the donor fragment on the catalytic activity has also been observed in previous transfer hydrogenation mechanistic studies.^{23b} Although in this case it could have a similar origin, the ultimate reason for the reactivity enhancement by the substituent in the N-alkylation process remains unclear.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

‡ Footnotes

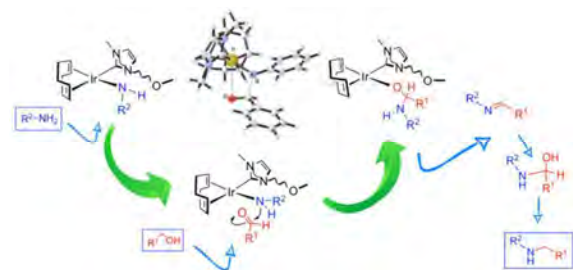
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Graphical Abstract

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